CHAPTER-VI

SYNTHESIS OF 2-ARYLIMINO THIAZOL 
[4,5-e] (1,4) DIAZEPINES
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SYNTHESIS OF 2-ARYLIMINO THIAZOL [4,5-e] (1,4) DIAZEPINES

1. INTRODUCTION:

Benzodiazepine and diazepine, class of heterocyclic compounds, are known to exhibit various biological activities\textsuperscript{1-9}, such as antipyretic, analgesic, sedative, antiasthmatic and antidepressant. 1,4-Benzodiazepines have been intensively studied since the early 1960's because of their value in psychotherapy and an impressive armoury of synthetic routes\textsuperscript{10,11}.

Benzodiazepines also possess a wide variety of pharmacological properties\textsuperscript{12}. Some of the benzodiazepine derivatives synthesized by Shanthan Rao \textit{et al}\textsuperscript{13} have shown anticancer activity in the preliminary experiments. The benzodiazepines introduced as antianxiety drugs have been proved useful as anticonvulsant, particularly diazepam (1) and nitrazepam (2).

![Structural diagrams](image)

Other benzodiazepines used as antianxiety agents include Oxazepam (3) R=H, \textit{\textalpha} lorazepam (3) R=Cl and potassium chlorazepate (4).

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The benzodiazepines also possess other therapeutic applications, many being used to induce sleep, diazepam and nitrazepam are anticonvulsants, and flurozepam (5) is both an antianxiety agent and a potent hypnotic.

Thieno-and Pyrazolo-1, 4-diazepinones isosteric with diazepam have similar pharmaceutical properties.¹⁴

The discovery of benzodiazepine (6) has opened a new era in the research of central nervous system and the drugs acting on it. Benzodiazepines constitute a class of centrally acting drugs with a wide range of therapeutic applications. They can be used as anxiolytics, hypnotics, sedatives, anticonvulsants, muscle relaxants etc.¹⁵
One of the first active members of this class of compounds was synthesised as chlorodiazepoxide (7). It was rapidly followed by the preparation of diazepam (1). The N-methyl analogue of its degradation product was used in early structural elucidation work.

**Synthesis of Benzodiazepines:**

In view of the useful biological activities, pharmacological properties and therapeutic applications of benzodiazepines, various methods have been developed for their synthesis. Some of the important methods are described in the Schemes I to VI.

2, 3-dihydro-1, 4-diazepine\(^{17}\) can be obtained by reaction of ethylenediamine and its N-alkyl N,N'-dialkyl and N,N'-diaryl analogues with 1,3-dialdehyde or diketones (Scheme I).
α, β-unsaturated and β-halogeno aldehydes and Ketones on reaction with o-phenylenediamine give dihydro benzodiazepine\textsuperscript{18-21} (Scheme II).

1,4-Benzodiazepines\textsuperscript{19} may be prepared via displacement of the activated halogen in reaction with 2-halogeno -5-nitroacetophenones with 1, 2-diamines (Scheme III).

Bischler-Napieralsky cyclization can be used to form 1, 4-benzodiazepines\textsuperscript{19} (Scheme IV). The enediimine underwent high yielding thermal transformation to cyclic product via an intramolecular enamine addition in the intermediate\textsuperscript{22} (Scheme V).

Quinazolinium salt or its 4-Oxo analogue, on treatment with diazoalkanes, also undergo ring expansion to give 1, 4-benzodiazepines\textsuperscript{23} (Scheme VI).

The clinical importance and commercial success of 1,4-benzodiazepines has led to extensive synthetic studies on related compounds in the hope of finding agents that would be more specific for various kinds of CNS disturbances. Many analogues have been synthesized in which the benzene ring has been replaced by a heterocyclic moiety and for these the synthetic methods used often closely resemble those used for benzodiazepines\textsuperscript{10,11}.

Recently, attention has been concentrated on the synthesis of analogues having heterocycles in place of the benzene ring and on compounds having additional fused heterocyclic rings. In contrast, monocyclic 1, 4-diazepines, with the exception of the
1) Method due to D. Lloyd et al. (1974):

\[
\begin{align*}
\text{NH}_2 & \quad \text{O} = \text{C} \quad \text{Me} \\
\text{NH}_2 & \quad \text{O} = \text{C} \quad \text{Me}
\end{align*}
\]

\[
\begin{array}{c}
\text{Me} \\
\text{Me}
\end{array}
\]

\[
\text{Scheme I}
\]

2) Method involving condensation of \( \alpha, \beta \) unsaturated aldehydes and ketones with o-phenylenediamine:

\[
\begin{align*}
\text{NH}_2 & \quad \text{R}_1 \quad \text{CH} \\
\text{NH}_2 & \quad \text{R}_2
\end{align*}
\]

\[
\begin{array}{c}
\text{Me} \\
\text{R}_1
\end{array}
\]

\[
\text{Scheme II}
\]

3) Method due to Archer and L.H. Sternbach (1968):

\[
\begin{align*}
\text{Cl} & \quad \text{H}_2 \text{N} - \text{CH}_2 - \text{CH}_2 - \text{NH}_2 \\
\text{CO} - \text{Ph} & \quad \text{0}_2 \text{N}
\end{align*}
\]

\[
\text{Scheme III}
\]
4) Bischler-Napieralsky, Cyclization\textsuperscript{19} (1968).

\begin{center}
\includegraphics[width=0.5\textwidth]{Scheme_IV}
\end{center}

\textbf{Scheme IV}

5) Method due to A. Padwa and S. I. Welmore\textsuperscript{22} (1972).

\begin{center}
\includegraphics[width=0.5\textwidth]{Scheme_V}
\end{center}

\textbf{Scheme V}


\begin{center}
\includegraphics[width=0.5\textwidth]{Scheme_VI}
\end{center}

\textbf{Scheme VI}
interesting 2, 3-dihydro-1,4-diazepine system\(^2\) have received scant attention in recent years, and it is yet difficult to prepare a fully unsaturated system. In view of these reports and in continuation of our work in the synthesis of fused five, six and seven membered heterocyclic diazepines, we report synthesis of 1, 4-diazepine type of compounds using two different routes.

**VI 2. PRESENT WORK:**

On the basis of these findings it was decided to condense carboxaldehydes (4 a-f) synthesized in chapter II with equimolar quantities of ethylenediamine with the hope to get 2-arylimino-thiazol [4, 5-e] (1,4) ethylenediazepines (9a-f) of interesting biological activities.

Mosher et al.,\(^{25}\) have condensed 6-acetyl-5H-1-pyridine-5,7 (6H)-dione Ia with ethylenediamines. This reaction yielded two different types of products depending upon the reaction conditions. Additions of Ia (1 mol) to a refluxing ethanolic solution of ethylenediamine (1.5 mol) in the presence of formic acid resulted into 6-[1-(2-aminoethylimino) ethyl] -5H-1-pyridine-5,7 (6H)-dione (II) in good yields.

Reverse addition of the reactants, ethylenediamine to a refluxing ethanolic solution of Ia and change of their molar ratio gave the 1:2 product 6, 6'- [ethylene bis (nitriloethylidyne)] di-5H-1-pyridine-5,7 (6H)-dione (VI) in very good yields.

When compound II was heated for 12 hours in refluxing 1-propanol in the presence of formic acid, the expected ring
closer took place with the formation of only one of the two possible isomers 2, 3-dihydro-5-methylpyrido[2',3':4,3] cyclopenta [2, 1-e] [1,4] diazepine 6(1H) - one (IV).

Similar type of ring closer was also observed in the reaction of 2-acetyl-1, 3-indandione with ethylenediamine, and in the reaction of 6-benzoyl-5H-1-pyridine-5, 7 (6H)-dione with hydrazine.

Addition of 6-benzoyl-5H-1-pyridine-5,7 (6H)-dione (Ib) to a refluxing solution of o-phenylenediamine in 2-propanol in the presence of formic acid yielded directly 6-phenylbenzo [b] pyrido [2', 3': 4,3] cyclopenta-[2, 1-e] [1,4] diazepin-7 (12H)-one (VII). Refluxing time required for this reaction was 24 hours (Scheme VII).

The formation of seven membered rings is rather difficult because both strain and distance factors become worse in this case. Due to this reason extraordinary conditions such as pH control and refluxing the reaction mixture for longer duration is required for the formation of such seven membered rings.

VI.3. PREPARATION OF 2-ARYLIMINOTHIAZOL [4,5-e] (1,4) DIAZEPINES BY ROUTE I:

The method described by Mosher et al. was used for the conversion of intermediate carboxaldehyde (4a-f) into 2-aryl-
iminothiazol [4,5-e] (1,4) diazepine (9a-f). In this method a suspension of carboxaldehyde (4a-f) in n-propanol was added to equimolar amount of ethylenediamine maintaining acidic pH of the
Scheme VII

a, R = CH₃
b, R = Ph
solution by adding formic acid and refluxing reaction mixture for 16 hours. The yields of the products (9a-f) were found only in the range of 49-59%.

The scheme and general mechanism visualised are as shown in Scheme VIII.

The method described in route-I requires critical pH control and refluxing time is 16 hours. In addition to these tedious and time consuming reaction conditions, the yields of the products obtained were only in the range of 49 to 59%. In order to increase the percentage yield and to simplify reaction conditions it was decided to develop a convenient and less time consuming method for the synthesis of 2-arylimino thiazol [4,5-e] (1,4) diazepine (9a-f) which could then be generalised. For this purpose it was first decided to synthesise iodocarboxaldehydes (8a-f) from chlorocarboxaldehydes (4a-f). The chlorocarboxaldehydes (4a-f) possess chlorine as the poor leaving group. Therefore, it was replaced by better leaving group iodine to afford iodocarboxaldehydes. This nucleophilic substitution reaction is favourable as iodide ion is a better nucleophile than chloride ion which can be easily replaced. The intermediate iodocarboxaldehydes can be cyclised into seven membered heterocyclic dizepines by refluxing with equimolar quantities of ethylenediamine in ethanol. The strategy visualised is shown in Scheme IX.
Refluxed in n-propanol (16 hours)

Scheme VIII

Scheme IX
VI. 4. PREPARATION OF 2-ARYLIMINO THIAZOL [4,5-e] (1,4) DIAZEPINES

BY ROUTE II:

The chlorocarboxaldehyde 4a, when refluxed with NaI and aq. HCl in the presence of acetonitrile an orange coloured compound 4-iodo-2-phenylaminothiazole-5-carboxaldehyde 8a, m.p. 205°C, was formed. IR spectrum of 8a (Fig. I) showed bands at 500, 530 and 570 cm⁻¹ typical for C-I stretching frequency. A band at 1700 cm⁻¹ for carbonyl and at 2920 cm⁻¹ for C-H stretching frequency for aldehyde group was also found present. The presence of iodine was confirmed by sodium fusion test.

The chlorocarboxaldehyde 4b, when refluxed with NaI and aq. HCl in acetonitrile yielded an orange coloured compound, 4-iodo-2-(2-methylphenylamino) thiazole-5-carboxaldehyde 8b, m.p. 205°C. This compound showed significant bands in its IR spectrum at 500 and 580 cm⁻¹ for C-I stretching and 1700 cm⁻¹ for carbonyl frequency of aldehyde group.

Similar reaction of chlorocarboxaldehyde 4c, with NaI and aq. HCl gave 4-iodo-2-(4-methyl phenylamino) thiazole carboxaldehyde 8c, having m.p. 165-166°C. The assigned structure 8c was supported by its IR spectrum (Fig. I-2). Two bands at 500 and 580 cm⁻¹ indicated the presence of C-I band. Carbonyl group was shown by a band at 1700 cm⁻¹, and a band at 2800 cm⁻¹ was assigned to C-H stretching of aldehyde group. Usual sodium fusion test also confirmed the presence of iodine.
Fig. I-1: IR spectrum of 4-iodo-2-phenyl amino thiazole-5-carboxaldehyde (8a)
Fig. I-2: 4-iodo-2-(4-methylphenylamino)thiazole-5-carboxaldehyde (8c).
When chlorocarboxaldehyde 4d and 4e were refluxed with NaI and aq. HCl in acetonitrile, it gave an orange coloured 4-iodo-2-(2-chlorophenylanino) thiazole carboxaldehyde 8d, m.p. 213°C and a dark orange coloured 4-iodo-2-(4-chlorophenylamino) thiazole carboxaldehyde 8e, m.p. 210-215°C respectively.

When intermediate chlorocarboxaldehyde 4f was refluxed with NaI and aq. HCl in acetonitrile yielded dark brown coloured 4-iodo-2-(4-methoxyphenylamino) thiazole-5-carboxaldehyde, 8f having m.p. 225°C. The assigned structure 8f was supported by its IR spectrum. Presence of iodine was confirmed by usual sodium fusion test.

\[
\begin{align*}
\text{CHO} \\
\text{R}_1 = & \text{H} \quad \text{and} \quad \text{R}_2 = \text{H} \\
\text{R}_1 = & \text{CH}_3 \quad \text{and} \quad \text{R}_2 = \text{H} \\
\text{R}_1 = & \text{H} \quad \text{and} \quad \text{R}_2 = \text{CH}_3 \\
\text{R}_1 = & \text{Cl} \quad \text{and} \quad \text{R}_2 = \text{H} \\
\text{R}_1 = & \text{H} \quad \text{and} \quad \text{R}_2 = -\text{OCH}_3
\end{align*}
\]

An equimolar mixture of 4-iodo-2-phenylamino thiazole 5-carboxaldehyde, 8a and ethylenediamine was refluxed in anhydrous ethanol which yielded a dark brown coloured compound, 9a, m.p. 170°C. In IR spectrum (Fig. 1-9) peaks at 500, 530 and 570 cm\(^{-1}\) observed in starting compound 8a, were found absent in 9a indicating the disappearance of C-I bond. Similarly, the disappearance of peaks at 1700 cm\(^{-1}\) and 2820 cm\(^{-1}\) indicated the
Fig. I-3: IR spectrum of 2-phenylimino thiazol[4,5-e](1,4)ethylenediazepine (9a).
absence of aldehyde group. Absence of -CHO group was also confirmed by treating 9a with 2:4 DNP reagent which did not produce any coloured compound. Hence it was concluded that the -CHO group has taken part in the condensation reaction. Other bands observed in IR spectrum are 1370, 1460 and 1520 cm⁻¹ which could be attributed to C—N, C—N and C—C. Absence of iodine was also indicated by usual sodium fusion test. Elemental analysis suggested C₁₂H₁₂N₄S as the molecular formula. Thus from IR spectral data, chemical tests and elemental analysis, structure 9a was assigned to the compound. Other possible structures 10, 11 and 12 were ruled out on the basis of absence of iodine in microanalysis and absence of C—I band in IR spectra.

An equimolar mixture of 4-iodo-2-(2-methylphenylamino) thiazole-5-carboxaldehyde 8b and ethylenediamine was refluxed in anhydrous ethanol, it gave 9b as dark brown coloured compound, m.p. 200°C. IR spectrum (Fig. I-4) of 9b showed the absence of peaks at 500, 580 cm⁻¹ indicating the disappearance of C—I bond. Similarly, the absence of carbonyl peak at 1700 cm⁻¹ and C—H stretching of -CHO group around 2800 cm⁻¹ was found absent. It indicated that the aldehyde group has undergone condensation reaction. The absence of iodine was also detected by usual sodium fusion test. Elemental analysis suggested C₁₃H₁₄N₄S as the molecular formula.

In the PMR spectrum of 9b (in CDCl₃) four protons appeared in aromatic region at 7.5 δ as a multiplet and three methyl protons attached to the benzene ring appeared at 2.30 δ as a singlet.
Fig. I-4: IR spectrum of 2-(2-methylphenylimino)thiazol [4,5-e] (1,4) ethylenediazepine (9b).
Thus, the chemical tests, IR and PMR spectral data, coupled with elemental analysis suggested structure 9b to the compound.

Condensation of 1:1 mole of 4-iodo-2-(4-methylphenylamino)thiazole-5-carboxaldehyde, 8c and ethylenediamine in anhydrous ethanol yielded a brown coloured compound 9c, m.p. 100°C. Structure 9c was suggested to it on the basis of mode of formation. Elemental analysis also suggested C13H14N2S as the molecular formula. In the PMR spectrum (in CDCl3) four protons appeared in aromatic region at 7.5 δ as a multiplet, and three methyl protons appeared at 2.30 δ as a singlet attached to the benzene ring.

\[ \text{Structure } 9 \text{ a} \]
\[ \text{Structure } 10 \]
\[ \text{Structure } 11 \]
\[ \text{Structure } 12 \]
\[ b, R_1 = \text{CH}_3 \text{ and } R_2 = \text{H} \]
\[ c, R_1 = \text{H} \text{ and } R_2 = \text{CH}_3 \]
Similar condensation reaction of equimolar quantities of 4-iodo-2-(2-chlorophenylamino) thiazole-5-carboxaldehyde, 8d and ethylenediamine gave a faint yellow coloured compound 9d, m.p. 165°C.

When equimolar mixture of 4-iodo-2-(4-chlorophenylamino) thiazole-5-carboxaldehyde, 8e and ethylenediamine was refluxed in anhydrous ethanol, a yellow coloured compound 9e, m.p. 180-192°C was obtained. Elemental analysis showed C_{12}H_{11}N_{2}SCl as the molecular formula.

4-iodo-2-(4-methoxyphenylamino) thiazole-5-carboxaldehyde, 8f and ethylenediamine when refluxed in equimolar quantities in ethanol formed 9f as a dark brown coloured compound, m.p. 257-258°C.

Compound (9a-f) synthesised by Route-I and Route-II are the same. It is confirmed by their melting points and superimposable IR spectra. Fig. 1-5 shows the superimposable IR spectrum of 2-(4-methoxyphenylimino) thiazol [4,5-e] (1,4) ethylenediazepine (9f), synthesised by Route-I and Route-II.
Fig. I-5: IR spectra of 2-(4-methoxyphenylimino)thiazol [4,5-e] (1,4) ethylenediazepine (9f) synthesised by Route I & Route II (Superimposable)
CONCLUSION:

Thus, in this chapter, we have synthesised biologically important, seven membered heterocyclic compounds, 2-arylimino-thiazol [4,5-e] (1,4) diazepines using two different routes.

By comparing the percentage yields of the products, time required for the synthesis and reaction conditions, we conclude that route II should be the preferred method for the synthesis of the above mentioned compounds.
EXPERIMENTAL
VI.5. EXPERIMENTAL:

Preparation of 2-arylimino thiazol [4,5-e] (1,4) diazepines (9a-f) by route I:

A mixture of chloroaldehyde (4a-f) (0.005 mole) and ethylenediamine (0.005 mole) in n-propanol (10 ml) was refluxed in a water bath for 16 hours. The pH of the reaction mixture was maintained between 3 and 5 by adding formic acid. The excess of solvent was removed by distillation. The reaction mixture was then slowly added to crushed ice with constant stirring. This yielded solid products. The crude compounds on recrystallization formed compounds (9a-f). The molecular formula, yield, colour and m.p.s are recorded in the Table No. 1.
Table No. 1

Properties of 2-arylimino thiazole (4,5-e) (1,4) diazepines (9a-f) obtained by Route-I.

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Molecular formula</th>
<th>Yield gms.</th>
<th>% of yield</th>
<th>Colour</th>
<th>m.p. °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>9a</td>
<td>(C_{12}H_{12}N_S)</td>
<td>0.600</td>
<td>49.00</td>
<td>Dark-brown</td>
<td>170</td>
</tr>
<tr>
<td>9b</td>
<td>(C_{13}H_{14}N_S)</td>
<td>0.700</td>
<td>54.00</td>
<td>Brown</td>
<td>198</td>
</tr>
<tr>
<td>9c</td>
<td>(C_{13}H_{14}N_S)</td>
<td>0.750</td>
<td>58.00</td>
<td>Dark-brown</td>
<td>104</td>
</tr>
<tr>
<td>9d</td>
<td>(C_{12}H_{11}N_SCl)</td>
<td>0.700</td>
<td>50.00</td>
<td>Yellow</td>
<td>162</td>
</tr>
<tr>
<td>9e</td>
<td>(C_{12}H_{11}N_SCl)</td>
<td>0.800</td>
<td>57.00</td>
<td>Dark-yellow</td>
<td>184</td>
</tr>
<tr>
<td>9f</td>
<td>(C_{13}H_{14}N_SO)</td>
<td>0.800</td>
<td>59.00</td>
<td>Brown</td>
<td>255</td>
</tr>
</tbody>
</table>
Preparation of 4-iodo-2-arylamino thiazole-5-carboxaldehydes (8a-f) :

1. Preparation of 4-iodo-2-phenylamino thiazole-5-carboxaldehyde (8a) :

Sodium iodide (2.0 g), 55% w/v aq. solution of HCl (0.5 ml) and acetonitrile (20 ml) was taken in a round bottom flask. To this mixture, 4-chloro-2-phenylamino thiazole-5-carboxaldehyde, 4a (1.180 g, 0.005 mole) was added. This reaction mixture was stirred under reflux for 4.5 hours. Most of the solvent (Ca.15 ml) was removed and water (Ca. 15 ml) and saturated aqueous solution of sodium carbonate were added to render the mixture alkaline. The crude product was filtered off, washed with water and dried in air. It was recrystallised with ethanol which formed an orange coloured compound (8a), 1.2 g (73%) m.p. 205°C.

IR (in nujol) :
500, 530, 570 cm⁻¹ (C-I stretching).
1700 cm⁻¹ (carbonyl group of aldehyde).
A mixture of sodium iodide (2 g.) 55% W/v aq. solution of HCl (0.5 ml) and acetonitrile (20 ml) was taken in a round bottom flask. To this mixture, 4-chloro-2-(2-methyl phenylamino) thiazole-5-carboxaldehyde 4b, (1.280 g., 0.005 mole) was added. This reaction mixture was stirred under reflux for 4.5 hours. Most of the solvent (Ca. 15 ml) was removed and water (Ca. 15 ml) and saturated aqueous solution of sodium carbonate were added to render the mixture alkaline. The crude product was filtered off, washed with water and dried in air. It was recrystallised with ethanol which yielded orange coloured compound 8b, 1.3 g. (76%) having m.p. 205°C.

IR (in nujol):

500, 580 cm⁻¹ (C-I stretching)
1700 cm⁻¹ (carbonyl group of aldehyde).

Preparation of 4-iodo-2-(2-methyl phenylamino) thiazole-5-carboxaldehyde (8c).

A mixture of sodium iodide (2 g.), 55% W/v aq. solution of HCl (0.5 ml) and acetonitrile (20 ml) was taken in a round bottom flask. To this mixture, 4-chloro-2-(4-methyl phenylamino) thiazole carboxaldehyde, 4c (1.260 g., 0.005 mole) was added. This reaction mixture was stirred under reflux for 4.5 hours. Most of the solvent (Ca. 15 ml) was removed and water (Ca. 15 ml) and saturated aqueous solution of sodium carbonate were added to render the
mixture alkaline. The crude product was filtered off, washed with water and dried in air. It was recrystallised with ethanol which yielded a brown coloured compound 8c, 1.4 g. (82%) having m.p. 165-166°C.

IR (in nujol):
500 and 580 cm⁻¹ (C-I stretching)
1700 cm⁻¹ (carbonyl group of aldehyde).

(D1) Preparation of 4-iodo-2-(2-chlorophenylamino) thiazole-5-carboxaldehyde (8d).

A mixture of sodium iodide (2 g.), 55% W/v aq. solution of HCl (0.5 ml) and acetonitrile (20 ml) was taken in a round bottom flask. To this mixture, 4-chloro-2-(2-chlorophenylamino) thiazole carboxaldehyde, 4d (1.365 g., 0.005 mole) was added. This reaction mixture was stirred under reflux for 4.5 hours. Most of the solvent (Ca. 15 ml) was removed and water (Ca. 15 ml) and saturated aqueous solution of sodium carbonate were added to render the mixture alkaline. The crude product was filtered off, washed with water and dried in air. It was recrystallised with ethanol which formed an orange coloured compound 12d, 1.4 g. (77%) having m.p. 213°C.

(E) Preparation of 4-iodo-2-(4-chlorophenylamino) thiazole-5-carboxaldehyde (8e).

A mixture of sodium iodide (2 g.), 55% W/v aq. solution of HCl (0.5 ml) and acetonitrile (20 ml) was taken in a round bottom flask. To this mixture, 4-chloro-2-(4-chloro phenylamino) thiazole
carboxaldehyde, 4e (1.365 g. 0.005 mole) was added. This reaction mixture was stirred under reflux for 4.5 hours. Most of the solvent (Ca. 15 ml) was removed and water (Ca. 15ml) and saturated aqueous solution of sodium carbonate were added to render the mixture alkaline. The crude product was filtered off, washed with water and dried in air. It was recrystallised with ethanol which yielded a brown coloured compound 8e, 1.5 g. (82%) having m.p. 210-215°C.

**[F] Preparation of 4-iodo-2-(4-methylphenylamino) thiazole-5-carboxaldehyde (8f).**

A mixture of sodium iodide (2 g.), 55% W/v aq. solution of HCl (0.5 ml) and acetonitrile (20 ml) was taken in a round bottom flask. To this mixture, 4-chloro-2-(4-methylphenylamino) thiazole carboxaldehyde, 4f (1.340 g. 0.005 mole) was added. This reaction mixture was stirred under reflux for 4.5 hours. Most of the solvent (Ca. 15 ml) was removed and water (Ca. 15ml) and saturated aqueous solution of sodium carbonate were added to render the mixture alkaline. The crude product was filtered off, washed with water and dried in air. It was recrystallised with ethanol which formed a dark brown coloured compound 8f, 1.5 g. (84%) having m.p. 225°C.

**IR (in nujol)**:

- 540 cm\(^{-1}\) (C-I stretching)
- 1720 cm\(^{-1}\) (carbonyl group of aldehyde).
Preparation of 2-aryl iminothiazol [4, 5-e] (1, 4) ethylenediazepines (9a-f).

A mixture of 4-iodo-2-phenylamino thiazole-5-carboxaldehyde 8a (0.660 g. 0.002 mole), ethylenediamine (0.12 g. 0.002 mole) in anhydrous ethanol (8 ml) was refluxed for 1.5 hours. The excess solvent was removed by distillation. The reaction mixture was then poured into crushed ice with constant stirring, which formed a dark brown coloured compound. The crude compound was then recrystallised from aqueous ethanol to form 9a, yield 0.300 g. (61%), m.p. 170°C.

Elemental analysis:

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>H</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Found</td>
<td>58.86%</td>
<td>5.12%</td>
<td>22.70%</td>
</tr>
<tr>
<td>Calculated for C_{12}H_{12}N_{4}S</td>
<td>58.01%</td>
<td>4.82%</td>
<td>22.85%</td>
</tr>
</tbody>
</table>
IR (in nujol) : 720 cm⁻¹, 1370 cm⁻¹, 1460 cm⁻¹, 1520 cm⁻¹ and 1600 cm⁻¹.

[B] Preparation of 2-(2-methylphenylimino) thiazol [4,5-e] (1,4) ethylenediazepine (9b).

A mixture of 4-iodo-2-(2-methylphenylamino) thiazole-5-carboxaldehyde, 8b (0.688 g. 0.002 mole), ethylenediamine (0.12 g., 0.002 mole) in anhydrous ethanol (8 ml) was refluxed for 1.5 hours. The excess solvent was removed by distillation. The reaction mixture was then poured into crushed ice with constant stirring, which formed a dark brown coloured compound. The crude product was then recrystallised from aqueous ethanol to form 9b, yield 0.350 g. (68%), m.p. 200°C.

**Elemental analysis:**

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>H</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Found</td>
<td>60.26%</td>
<td>5.31%</td>
<td>21.85%</td>
</tr>
<tr>
<td>Calculated for C₁₉H₁₄N₄S</td>
<td>60.46%</td>
<td>5.43%</td>
<td>21.70%</td>
</tr>
</tbody>
</table>

IR (in nujol) : 760, 1380, 1520, and 1620 cm⁻¹.

PMR in CDCl₃

2.35 δ S 3H CH₃ attached to benzene

7.50 δ m 4H Aromatic protons (Ar-H).

[C] Preparation of 2-(4-methylphenylimino) thiazol [4,5-e] (1,4) ethylenediazepine (9c).

A mixture of 4-iodo-2-(4-methylphenylamino) thiazole-5-carboxaldehyde, 8c (0.688 g. 0.002 mole), ethylenediamine (0.120 g., 0.002 mole) in anhydrous ethanol (8 ml) was refluxed for 1.5
hours. The excess solvent was removed by distillation. The reaction mixture was then poured into crushed ice with constant stirring, which formed a brown coloured compound. The crude product was then recrystallised from aqueous ethanol to form 9c, yield 0.400 g (78%), m.p. 100°C.

Elemental analysis:

Found

C 60.65%  H 5.66%  N 21.58%

Calculated for C_{19}H_{14}N_{4}S

C 60.46%  H 5.43%  N 21.70%

PMR in CDCl₃,

2.30 δ S 3H CH₃ protons attached to benzene
7.50 δ m 4H Ar-H

[D] Preparation of 2-(2-chlorophenylimino) thiazol [4,5-e] (1,4) ethylenediazepine (9d).

A mixture of 4-iodo-2-(2-chlorophenylamino) thiazole-5-carboxaldehyde, 8d (0.729 g, 0.002 mole), ethylenediamine (0.120 g, 0.002 mole) in anhydrous ethanol (8 ml) was refluxed for 1.5 hours. The excess solvent was removed by distillation. The reaction mixture was then poured into crushed ice with constant stirring, which formed a dark brown coloured compound. The crude product was then recrystallised from aqueous ethanol to form 9d, yield 0.350 g (63%), m.p. 165°C.

Elemental analysis:

Found

C 51.60%  H 3.80%  N 20.15%

Calculated for C_{12}H_{11}N_{4}S Cl

C 51.71%  H 3.85%  N 20.10%
[E] Preparation of 2-(4-chlorophenylimino) thiazol [4,5-e] (1,4) ethylenediazepine (9e).

A mixture of 4-iodo-2-(4-chlorophenylamino) thiazole-5-carboxaldehyde, 8e (0.728 g. 0.002 mole), ethylenediamine (0.12 g. 0.002 mole) in anhydrous ethanol (8 ml) was refluxed for 1.5 hours. The excess solvent was removed by distillation. The reaction mixture was then poured into crushed ice with constant stirring, which formed a dark brown coloured compound. The crude compound was then recrystallised from aqueous ethanol to form 9e, yield 0.400 g. (72%), m.p. 190-102°C.

Elemental analysis:

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>H</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Found</td>
<td>51.82%</td>
<td>4.08%</td>
<td>19.82%</td>
</tr>
<tr>
<td>Calculated for $C_{12}H_{11}N_{4}Cl$</td>
<td>51.71%</td>
<td>3.95%</td>
<td>20.10%</td>
</tr>
</tbody>
</table>

[F] Preparation of 2-(4-methoxyphenylimino) thiazol [4,5-e] (1,4) ethylenediazepine (9f).

A mixture of 4-iodo-2-(4-methoxyphenylamino) thiazole-5-carboxaldehyde, 8f (0.720 g. 0.002 mole), ethylenediamine (0.12 g. 0.002 mole) in anhydrous ethanol (8 ml) was refluxed for 1.5 hours. The excess solvent was removed by distillation. The reaction mixture was then poured into crushed ice with constant stirring, which afforded a dark brown coloured compound. The crude compound was then recrystallised from aqueous ethanol to form 9f, yield 0.350 g. (64%), m.p. 257-258°C.

Elemental analysis:

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>H</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Found</td>
<td>56.72%</td>
<td>5.02%</td>
<td>20.24%</td>
</tr>
<tr>
<td>Calculated for $C_{19}H_{14}N_{4}SO$</td>
<td>56.93%</td>
<td>5.11%</td>
<td>20.43%</td>
</tr>
</tbody>
</table>
REFERENCES
CHAPTER - VI

REFERENCES

5. S. Guenther, E. Guenther and F. Sigfrid, Ger. offen, 2,624, 811 (Cl. CO 7D, A 61 k) 1974; Chem. Abstr., 84, 90189e (1976).


